REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 1-5 remain pending and are presented for further examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking a substantial asserted utility or a well-established utility for the reasons set forth in the previous Office Actions. The PTO asserts that one skilled in the art would not know how to use the claimed invention. According to the PTO, "[t]he data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO1069 polypeptide nor any particular biological activity of the polypeptide." Office Action at 3. The PTO relies on Hu *et al.* and other references for the propositions that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that what is often seen is a lack of correlation between DNA expression and increased peptide levels. The PTO argues that further research is required to determine whether the PRO1069 polypeptide is differentially expressed, making the asserted utility for the claimed antibodies not substantial.

Applicants have previously set forth the legal standard for utility. It is established that the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not

those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants first offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly kidney tumors. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1069 polypeptide is expressed at least two-fold higher in normal kidney tissue compared to kidney tumor tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the mRNA for the PRO1069 polypeptide is differentially expressed in kidney tumor tissue compared to normal kidney tissue, it is more likely than not that the PRO1069 polypeptide is likewise differentially expressed in these tumors; and antibodies that specifically bind the PRO1069 polypeptide are therefore useful as a diagnostic tool to distinguish kidney tumor tissue from normal kidney tissue.

Applicants understand the PTO to be asserting that "[t]he data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO1069 polypeptide nor any particular biological activity of the polypeptide" and that "the skilled artisan would need to perform additional experiments to reasonably confirm" that the PRO1069 polypeptide is differentially expressed in kidney tumor.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." *M.P.E.P.* § 2107.02 III B. The references cited by the PTO in support of its rejections are either irrelevant, not contrary to Applicants' arguments, or actually offer support for Applicants' position. Even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is more

likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The standard is not absolute certainty.

Applicants have established that the Gene Encoding the PRO1069 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

The PTO begins by questioning the data provided in Example 18 of the specification: "The instant specification does not disclose that PRO1069 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu, the skilled artisan would not reasonably expect that PRO1069 protein can be used as a cancer diagnostic." Office Action at 6.

Applicants first remind the PTO of the level of evidence required to support a substantial utility.

> [T]he Appellant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the Appellant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (emphasis in original, citations omitted).

The Court of Appeals for the Federal Circuit has stated that the standard for satisfying the utility requirement is a low one:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. *See Brenner v. Manson,* 383 U.S. 519, 534, 86 S.Ct. 1033, 16 L.Ed.2d 69 (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger,* 120 F. 274, 275 (7th Cir.1903) (test for utility is whether invention "is incapable of serving any beneficial end"). *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364, 1366, 51 U.S.P.Q. 2d 1700 (Fed. Cir. 1999) (emphasis added).

The low threshold for satisfying the utility requirement is reflected in the standard set by the Federal Circuit for invalidating a patent based on a lack of utility: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack

of utility. Some degree of utility is sufficient for patentability. Further, the defense of non-utility cannot be sustained without proof of total incapacity." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473 (Fed. Cir. 1984) (emphasis added, citations omitted).

Because the standard for satisfying the utility requirement is so low, requiring total incapacity for a finding of no utility, the M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been *rarely* sustained by federal courts. Generally speaking, in these *rare* cases, the 35 U.S.C. 101 rejection was sustained [] because the Appellant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (C.C.P.A. 1967) (underline emphasis in original, italic emphasis added).

In *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the court held that crude screens for pharmacological activity which were reported as qualitative results without statistical analysis were sufficient to establish utility. The Appellants in *Nelson* relied on two tests to prove practical utility for derivatives of naturally occurring prostaglandins: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, responses to the compounds were categorized qualitatively, as either a depressor (lowering) effect or a pressor (elevating) effect. *Nelson*, 626 F.2d at 854-55. In the GC-SMS test a section of colon was excised from a freshly-killed gerbil for suspension in a physiological solution, and a lever arm was connected to the colon in such a way that any contraction was recorded as a polygraph trace. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as "rough screens, uncorrelated with actual utility." *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board "erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use." *Id.* (emphasis added). The Court stated that "practical utility" was characterized as a use of the claimed discovery in a manner which provides some immediate benefit to the public, establishing the rule that "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public.... [W]e conclude that adequate proof of any such activity constitutes a showing of practical utility." *Id.* (emphasis added).

The Court rejected Bowler's argument that the BP and GC-SMS tests are inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court stated that "a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Id.* (emphasis added). The Court concluded that a "reasonable correlation" between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857.

The test articulated in *Nelson* is certainly met by the evidence in Example 18. Presented with the data in Example 18, one of skill in the art would find that there is a "reasonable correlation" between the observed property of differential expression in certain tumors and the suggested use as a diagnostic tool for cancer. In *Nelson* the fact that the results were qualitative, not statistically significant, and preformed *in vivo* in rats or *in vitro* on gerbil colon did not matter. The Court held that statistically significant results are not required, nor is it necessary to prove actual clinical therapeutic usefulness.

The gene expression data in the specification, Example 18, shows that the mRNA associated with the PRO1069 polypeptide was more highly expressed in normal kidney tissue compared to kidney tumor tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1069 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

With respect to the PTO's concerns regarding the data in Example 18, Applicants maintain that the methodology used to compare mRNA levels in normal tissue to that in cancerous tissue is reliable. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a

two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO rejects the Grimaldi declaration on the grounds that "Mr. Grimaldi has an interest in the present case as he is an invention [*sic*] in the present application and is employed by the assignee." Office Action at 4. Applicants note that an affidavit cannot be disregarded solely because it is signed by the applicant. (See M.P.E.P. §716.01(c)). Furthermore, Applicants maintain that Mr. Grimaldi's first Declaration objectively sets forth the methodology employed in the experiments described in Example 18 and the conclusions derived therefrom.

Further, Applicants submit that a lack of known role for PRO1069 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. The PRO1069 gene can be used as a cancer diagnostic tool because it is differentially expressed in kidney tumors.

In sum, the data in Example 18 are sufficient to establish a practical utility for the claimed invention. Applicants are asserting that the PRO1069 gene, polypeptide and antibodies have utility as diagnostic tools for cancer, particularly kidney tumor. Applicants are not asserting that the PRO1069 gene, polypeptide and antibodies necessarily provide a definitive diagnosis of

cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of kidney tumor. Statistically significant results are not required, nor is it necessary to prove actual clinical therapeutic usefulness.

While it is true that the specification provides only mRNA expression data, as Applicants explain in detail below, one of skill in the art would accept that increases or decreases in mRNA level for a particular gene are reasonably correlated with increases or decreases in the encoded polypeptide level, respectively. Therefore, there is a clear nexus between the differential expression of PRO1069 mRNA in kidney tumors and the differential expression of the PRO1069 polypeptide.

Hu et al., LaBaer and Winstead

Applicants next turn to the PTO's arguments based on Hu *et al.* and LaBaer. As previously pointed out, Hu et al. used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a published role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a published or known role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and

reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

More importantly, Hu did not look for a correlation between changes in mRNA and changes in protein levels, and therefore is not contrary to Applicants' assertion that there is a correlation between the two. Applicants are not relying on any "role" that PRO1069 has in cancer for their asserted utility. Instead, Applicants are relying on the differential expression of PRO1069 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

The PTO also relies on the publication by LaBaer to broaden its interpretation of Hu. *Office Action* at 5-6. The PTO points to a statement in LaBaer that "reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between samples." Office Action at 5, citing *LaBaer* at 976.

LaBaer is an unreviewed letter to the editor by an author of the Hu *et al.* article describing the automated literature searching tool used in the Hu *et al.* reference discussed above. LaBaer provides no further evidence than that provided in Hu, and provides no evidence whatsoever to support the conclusion that the results of Hu are applicable to the diagnostic utility of differentially expressed genes. Importantly, like the Hu reference, LaBaer does not consider or offer any discussion of whether there is a correlation between changes in mRNA levels and changes in the level of the encoded protein.

In addition, it is important to note that Applicants' are not relying on microarray data as discussed in Hu and LaBaer: "In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" *Hu* at 405, left column, first paragraph (emphasis added); and in Winstead, cited by the PTO on page 13 of the Office Action: "For all the information gene microarrays provide, they reveal relatively little about proteins, the molecules that carry out most of the functions of a cell."

Instead, they are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics

5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines, just as discussed in LaBaer. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Kuo *et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu, LaBaer, and Winstead's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Moreover, LaBaer is silent regarding the reliability of pooled samples, and whether or not differential expression in pooled samples are susceptible to disease-independent differences between samples. LaBaer's conclusions regarding disease-independent differences between samples are not applicable in the instant case where normal human tissue and corresponding human tumor tissue samples were used. Accordingly, LaBaer suffers from the same defects discussed above with respect to Hu *et al.*

Nothing in either LaBaer or Hu or Winstead addresses Applicants' assertion that there is a correlation between changes in mRNA level and changes in the level of the encoded polypeptide. As such, they are not relevant to establishing whether the claimed polypeptides have utility based on the differential expression of the PRO1069 mRNA in kidney tumors.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1069 cDNA between kidney tumors and normal kidney tissue. Therefore, it follows that expression levels of the PRO1069 gene can be used to distinguish kidney tumor tissue from normal kidney tissue. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1069 polypeptide and associated antibodies can also be used to distinguish kidney tumor from normal kidney tissue.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between Changes in mRNA Levels and Changes in the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1069 polypeptide in kidney tumors, it is likely that the PRO1069 polypeptide is likewise differentially expressed in these tumors; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO's cited references are not contrary to Applicants' asserted utility

The PTO cites the reference by Hanna and Mornin (Pathology Assocs. Med. Labs. Tech. Update (Aug. 1999)) as showing that "gene amplification does not reliably correlate with polypeptide over-expression, and thus, the level of polypeptide expression must be tested empirically." Office Action at 6.

In fact, Hanna and Mornin teach exactly the opposite. Hanna teaches that immunohistochemistry (IHC) can be used to measure the amount of expressed protein, while fluorescent in situ hybridization (FISH) can be used to measure the level of gene amplification. *Hanna* at 1, left col., last ¶. Contrary to the Examiner's assertions, Hanna and Mornin state: "In general, FISH and IHC results correlate well." *Hanna* at 1, right column, final ¶ (emphasis added).

The authors do state that there is a subset of tumors where protein overexpression is seen without gene amplification, and gene amplification is seen without protein overexpression. While these results are not surprising – Applicants have acknowledged that other mechanisms of gene and protein regulation exist but are not the predominant mechanism of gene regulation – it is not clear that these exceptions are even contrary to Applicants' assertion that changes in mRNA levels lead to changes in protein levels. For example, an increase in transcription, *i.e.* increased mRNA levels, can occur in the absence of gene amplification (an increase in the number of copies of the gene in the genome). Consistent with Applicants' assertions, the increased level of mRNA would lead to protein overexpression without gene amplification.

Similarly, it is possible that a gene could be amplified but not have increased mRNA levels. In such cases, the absence of protein overexpression in the absence of increased mRNA levels also would not be contrary to Applicants' assertions.

Regardless of whether or not these exceptions are in fact contrary Applicants' assertions, it remains true that they are exceptions, and that "[i]n general, FISH and IHC results correlate well." Therefore, the Hanna and Mornin reference is not contrary to Applicants' assertion that changes in mRNA levels generally lead to changes in the level of the encoded polypeptide.

The PTO also cites Greenbaum *et al.* (Genome Biology, 2003; 4:117) for support for its arguments, stating that the author "cautions against assuming that mRNA levels are generally correlative of protein levels." *Office Action* at 9.

Greenbaum does not provide any support for the PTO's position. As for the discussion of published work on pp. 1173-1174, Greenbaum cites three references which allegedly found a poor or no correlation: Anderson and Seilhamer (Electrophoresis 1997; 18:533-537); Lichtinghagen *et al.* (European Urology 2002; 42:398-406); and Chen *et al.* (Mol. and Cell. Proteomics 2002; 1:304-313). In addition, Greenbaum reports a fourth reference which found a strong correlation: Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45). The three references cited by Greenbaum are not contrary to Applicants' assertion, and therefore Greenbaum does not offer the PTO any support for its position.

In the Anderson and Seilhamer article, the authors conducted a study that looked at static levels of mRNA and protein across different genes. *See Anderson and Seilhamer* (attached as Exhibit 2). A lack of correlation between static levels of mRNA and protein across different genes is not relevant to Applicants' assertions, and therefore Greenbaums' statements based on these experiments are irrelevant and do not support the PTO's rejection.

The second reference relied on by Greenbaum is Lichtinghagen *et al.*, stating that the reference shows no significant relationship between mRNA and protein for matrix metalloproteinases (MMPs 2 and 9) and the tissue inhibitor of metalloproteinase 1 (TIMP-1) in human prostate cancer. Lichtinghagen examined the level of MMP-2, MMP-9 and TIMP-1 in cancerous and non-cancerous parts of 17 human prostate samples at both the mRNA and protein level. The level of mRNA was determined using RT-PCR, and the level of protein was determined using quantitative zymography and ELISA. Lichtinghagen reports that comparing

non-cancerous to cancerous tissue, mRNA levels were decreased for MMP-2, and unchanged for MMP-9 and TIMP-1. *See Lichtinghagen* at Abstract (attached as Exhibit 3). In contrast, looking at the protein level, MMP-2 levels were unchanged, while MMP-9 expression was higher and TIMP-1 levels were lower. *Id.* Thus, Lichtinghagen reports that there was no correlation between mRNA levels and protein levels. *Id.*

First, it is important to note that of the three genes examined, only one (MMP-2) showed any change in mRNA expression levels between cancerous and non-cancerous tissues. While statistically significant, the change was small (approximately 33% decrease), far less than a two-fold change. It is therefore not surprising that the authors did not see a measurable change in the amount of MMP-2 protein.

For MMP-9 and TIMP-1, the authors report that there was no change in the level of mRNA, but there was a change in protein level. This apparent lack of correlation between mRNA and protein levels is not contrary to Applicants' assertion that a change in mRNA level generally leads to a change in protein level. Applicants are not attempting to predict the level of mRNA based on changes in protein level, and Applicants have not asserted that the only means for changing the level of protein is to change the amount of the encoding mRNA. Therefore a change in protein without a change in mRNA is not contrary to Applicants' assertions.

Second, the authors in Lichtinghagen note that in another study, researchers found a direct correlation between mRNA levels and protein levels for MMP-2 in prostate cancer. *See Lichtinghagen* at 403, col. 2, *citing* Stearns and Wang (Cancer Res. 1993; 53(4):878-83). In the Stearns and Wang reference cited in Lichtinghagen, the authors report differences in MMP-2 mRNA levels between cancerous, benign and normal stromal tissue from human prostate. The authors state that "[e]nzyme-linked immunosorbent assays demonstrated that the amounts of type IV collangenase protein [MMP-2 protein] correlated directly with the mRNA levels in the tumor tissue." *Stearns and Wang* at Abstract (abstract attached hereto as Exhibit 4). Therefore, contrary to the results reported in Lichtinghagen, at least one other study reports a good correlation between changes in mRNA and protein levels for MMP-2 in prostate cancer.

In conclusion, Lichtinghagen is not contrary to Applicants' assertion that generally, a change in mRNA level leads to a corresponding change in protein level. Lichtinghagen reported a single gene where an apparent change in mRNA did not result in a corresponding change in the

level of protein. However, the change in mRNA level was very small, and other researchers have reported a direct correlation between mRNA levels and protein levels for the same gene in human prostate samples. The two other genes examined by Lichtinghagen did not show a change in mRNA level, and therefore say nothing about Applicants' assertion. Therefore, Greenbaum's statements based on Lichtinghagen do not support the PTO's rejection.

The third reference relied on by Greenbaum is Chen, *et al.* In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. This measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed

(approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

Chen also reports a lack of correlation for some mRNA/protein pairs. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to

detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue offers no support for the PTO's position. Thus, Chen is not contrary to Applicants' assertion, and therefore Greenbaum's reliance on Chen cannot support the PTO's rejection.

In contrast to these three references which offer no or very little support for the PTO's position, Greenbaum also cites a reference by Orntoft *et al.* In that study the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Orntoft* at Abstract (attached hereto as Exhibit 5). The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

Thus, when considered as a whole, the references cited by Greenbaum actually support Applicants position since the three which report no correlation are either irrelevant or offer no or little support for the PTO's position, and the one which reports a correlation between changes in gene expression and protein expression reports a correlation for 39 out of 40 genes studied.

The PTO also discusses Haynes *et al.* (Electrophoresis 1998; 19(11):1862-71) and Gygi *et al.* (Mol. and Cell. Bio., Mar. 1999; 1720-1730) in support for its argument that mRNA levels are not predictive of protein levels. Applicants have discussed at length in previous responses why the Haynes and Gygi references are not relevant to the issue of whether changes in mRNA

level for a particular gene leads to changes in protein level. Applicants will not repeat their arguments here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to this issue, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes and Gygi discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. For example, in Experiment 1, if a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z, the ratio of the amount of proteins X:Y:Z would be 1:2:4, such that there is a correlation between static levels of mRNA and protein across genes. This is essentially what the cited references examined. In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the ratio of the amount of protein X in condition A:B would be 1:2, such that there is a correlation between the change in the level of mRNA and protein for a particular gene.

The PTO would like to argue that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong.

Applicants emphasize, and the PTO will recognize, that this is just a simplified illustration to demonstrate the difference between the two issues being examined. However, this illustration makes clear that even if there is no correlation in the first experiment looking at static levels across genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment.

The Examiner discusses the Alberts, Lewin, Zhigang, Meric, Jang, Hanash S [a] and Hanash et al. [b] references, stating that these references underscore the unpredictability in the art and disclose that the predictability of protein translation and its possible use as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Applicants have addressed these references at length in previous responses, and will not repeat their arguments here.

Taken as a whole, the references discussed by the PTO do not support the PTO's rejection of Applicants' assertion that more often than not, there is a correlation between changes in mRNA level and changes in the level of the corresponding protein. If anything, the cited references support Applicants' position.

Applicants' previously submitted supporting declarations and references

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994), and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of these teachings, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants' additional supporting references

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Ornstoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 6), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between

transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 7) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 8) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 9) used real-time quantitative PCR and immunohistochemistry to evaluate

cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 10) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 11) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level.

Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 12). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 13) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 14), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals

for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 15) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 16) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed above, Applicants have challenged the relevance of references such as Haynes *et al.* and Gygi *et al.*, which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 17) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 18) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 19) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 20) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 21) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 22) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 23) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin

D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 24) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 25). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1069 mRNA is differentially expressed in kidney tumor tissue, the PRO1069 polypeptide will likewise be differentially expressed in these tumors. This differential expression of the PRO1069 polypeptide makes the claimed antibodies useful as diagnostic tools for cancer, particularly kidney tumor.

The Arguments made by the PTO are not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading

textbooks in the field, and is supported by numerous references and the declarations of skilled experts.

Applicants' asserted utility is based on the assertion that changes in mRNA level generally result in corresponding changes in the level of the encoded protein. In rejecting this conclusion, the PTO has cited references by Hu *et al.*, Gygi *et al.*, and others.

As explained above, these references are largely irrelevant when determining whether Applicants' asserted utility is more likely than not true. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence, including two uncontested expert declarations, excerpts from three textbooks, and over 115 scientific articles, is more than sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1069 gene and polypeptide in kidney tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1069 polypeptide is differentially expressed in kidney tumor tissue compared to normal kidney tissue. These data are strong evidence that the PRO1069 gene and polypeptide are associated with kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1069 gene, polypeptide and antibodies with a specific

disease. The asserted utility as a diagnostic tool for cancer, particularly kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Applicants have addressed each of the PTO's supporting references and shown that they are either irrelevant, or taken as a whole, actually support Applicants' assertion that a change in mRNA level leads to a corresponding change in the level of the encoded protein. In addition, Applicants have submitted expert declarations, textbook excerpts, and over 115 scientific publications which support Applicants' asserted utility.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO1069 antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 1-5 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

The PTO also asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. According to the PTO, as discussed in connection with the utility rejection, "the art of Alberts, Lewin, Meric, Jang et al., Vallejo et al., Powell et al., Fu et al., Gygi et al., Haynes et al., Hanash S [a] and Hanash et al. [b], Winstead and Irving et al. underscores the unpredictability in the art and discloses that the predictability of protein translation and its possible use as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation." Office Action at 16. Thus, the PTO maintains that one of skill in the art could not predictably use the antibodies of the present claims as a diagnostic or therapeutic agent with a reasonable expectation of success.

As discussed above with respect to the utility rejection, Applicants maintain that, while there are some exceptions, in general differential expression levels of mRNA leads to differential protein expression levels. Accordingly, Applicants maintain that the references cited by the PTO are not contradictory to the general rule.

The specification teaches in detail how to make the claimed antibodies which specifically bind PRO1069. Likewise, the specification provides sufficient guidance as to how to use the claimed antibodies. Thus, contrary to the PTO's statement, there is significant guidance how to make and use the claimed antibodies. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of

non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide).

In view of the foregoing, Applicants maintain that the specification enables one skilled in the art to make and use the claimed invention.

Priority

Applicants acknowledge that the PTO has granted the present application priority to PCT/US00/23328, filed 24 August 2000.

Rejections under 35 U.S.C. § 102 – Anticipation

Claims 1-2 and 4-5 were rejected under 35 U.S.C. 102(a) on the assertion that they are anticipated by Lal et al. (WO 00/00610, 1/6/2000). According to the Examiner, Lal et al. teach a polypeptide (SEQ ID NO:35), which is identical to the polypeptide of SEQ ID NO:50 and antibodies that bind the polypeptide.

Applicants have previously submitted the Declaration of Goddard et al., originally submitted in related U.S. Patent Application Serial No. 10/063,555. The declaration establishes that the presently claimed subject matter was conceived prior to Lal's earliest priority date of June 26, 1998 and diligently reduced to practice thereafter. Applicants argued that therefore the cited reference is not available as prior art.

The PTO responds by saying that the rejection was made under 35 U.S.C. § 102(a) as of the publication date of January 6, 2000, therefore Applicants arguments pertaining to Lal's first provisional application "are not relevant." Office Action at 18. The PTO goes on to state that the "priority documents do not provide adequate written support for the quantitative PCR analysis of a cDNA library measuring mRNA expression (i.e. Example 18). For these same reasons, the Declaration of Goddard et al. filed on 10/14/2005 under 37 C.F.R. 1.131 has been considered but is ineffective to overcome the Lal reference." Office Action at 18.

35 U.S.C. § 102(a) states that a person is entitled to a patent unless "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, **before the invention thereof by the applicant**..." The M.P.E.P. states that "A rejection based on 35 U.S.C. 102(a) can be overcome by:... **Filing an affidavit or declaration under 37 CFR 1.131 showing prior invention**...." *See* M.P.E.P. § 706.02 (b). As

set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... **at least conception being at a date prior to the effective date of the reference**." *See* M.P.E.P. § 715.07. The showing of facts must be sufficient to show "**conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice.**" *See id.*

Applicants' 1.131 Declaration demonstrates that the claimed subject matter, more particularly antibodies which specifically bind to the polypeptide of SEQ ID NO: 50, was conceived by Applicants prior to January 6, 2000. Furthermore, as evidenced by the declaration and accompanying exhibits, Applicants exhibited diligence in reducing the subject matter of the claims to practice by performing various assays to confirm the function of the polypeptides recognized by the claimed antibodies. Specifically, the declaration states that the sequences of SEQ ID NOs:49 and 50 were first disclosed in U.S. Provisional Application 60/088740, filed June 10, 1998, as SEQ ID NOs:1-3, in Figures 1 and 2. Clearly, the polypeptide of SEQ ID NO:50 was conceived at least by the June 10, 1998 filing date of the provisional application as it is disclosed therein. In addition, antibodies to SEQ ID NO:50 and the remainder of the invention as presently claimed was also clearly conceived at least by the filing date of the provisional application, as a reading of the entire provisional application makes clear. For example, the provisional application states "[i]n another aspect, the invention concerns an isolated PRO1069 polypeptide, comprising an amino acid sequence having ... at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to 89, inclusive of Figure 2 (SEQ ID NO:3)." *Prov. Appl. No. 60/088740* at 4. The provisional application also states "[i]n another aspect, the invention concerns a PRO1069 extracellular domain comprising an amino acid sequence having ... at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to X of Figure 2 (SEQ ID NO:3), wherein X is any one of amino acid residues 32 to 41 of Figure 2 (SEQ ID NO:3)." *Id.* Also disclosed are the manufacture of antibodies to PRO1069, and their use to detect PRO1069 expression in specific tissue types. *See, e.g. Id.* at

26-32. Thus, contrary to the PTO's assertion, the provisional application clearly demonstrates conception of the invention by at least June 10, 1998, which is prior to the earliest date of Lal et al. Following conception, the evidence presented with Applicants' declaration demonstrates diligent reduction to practice as Applicants developed primers and probes to test for the differential expression of PRO1069.

Applicants have therefore provided a declaration showing prior invention of the claimed subject matter. The declaration establishes that the presently claimed subject matter was conceived prior to Lal's earliest priority date of June 26, 1998, and therefore also prior to the publication date of January 6, 2000, and diligently reduced to practice thereafter. Applicants have established prior invention by their 131 Declaration. This is sufficient to remove the cited reference as prior art.

Claims 1-2 and 4-5 were also rejected under 35 U.S.C. 102(e) on the assertion that they are anticipated by Walker et al. (U.S. Patent 6,277,574 B1, 4/9/1999). The PTO asserts that Walker et al. discloses a polypeptide (SEQ ID NO:11) that is identical to the polypeptide of SEQ ID NO:50 and monoclonal antibodies and antibody fragments that specifically bind the polypeptide.

The M.P.E.P. states that "A rejection based on 35 U.S.C. 102(e) can be overcome by:... **Filing an affidavit or declaration under 37 CFR 1.131 showing prior invention**...." *See* M.P.E.P. § 706.02 (b).

The PTO again asserts that the "the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications...do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression," and therefore rejects the Declaration of Goddard et al. filed under 37 C.F.R. 1.131. Office Action at 19.

As stated above, the 1.131 Declaration establishes that the presently claimed subject matter was conceived prior to the April 9, 1999 date for Walker et al., and diligently reduced to practice thereafter. Applicants have therefore established prior invention by their 1.131 Declaration. This is sufficient to remove the cited reference as prior art.

Rejection under 35 U.S.C. § 103 – Obviousness

Claims 1-5 were rejected under 35 U.S.C. 103(a) on the assertion that they are unpatentable over Walker et al. (U.S. Patent 6,277,57481, 4/9/1999) in view of Queen et al. (U.S. Patent 5,530,101, issued 6/96). The PTO maintains that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized antibody to the polypeptide of Walker et al. in view of Queen et al.

The PTO again states that the Declaration of Goddard et al. is "ineffective to overcome the Walker et al. reference." Office Action at 19. The PTO incorrectly reasons that because "the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications...do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression," the Declaration of Goddard et al. is ineffective to remove the cited reference as prior art.

As discussed above, Applicants have demonstrated conception of the claimed invention prior to the April 9, 1999 date which the PTO asserts for the Walker reference, together with diligence in reducing the invention to practice. Thus, Walker is not available as prior art. Applicants further maintain that the disclosure of humanized antibodies in Queen does not render the claimed antibodies obvious because there is no teaching or suggestion of antibodies which bind to the polypeptide of SEQ ID NO: 50 in Queen. Applicants therefore respectfully request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 7, 2006

By: _____
AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

2463631
032106